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Twenty-Year Survivors of Kidney Transplantation

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There have been few studies of patients with renal allografts functioning for more than 20 years. We sought to identify clinical factors associated with ultra long-term (>20 year) renal allograft survival and to describe the clinical features of these patients. We performed a retrospective analysis of the Irish Renal Transplant Database and included 1174 transplants in 1002 patients. There were 255 (21.74%) patients with graft function for 20 years or more. Multivariate analysis identified recipient age (HR 1.01, CI 1.01–1.02), gender (male HR 1.25, CI 1.08–1.45), acute rejection (HR 1.26, CI 1.09–1.45) and transplant type (living related donor vs. deceased donor) (HR 0.52, CI 0.40–0.66) as significantly associated with long-term graft loss. Median serum creatinine was 115 μmol/L. The 5-year graft survival in 20-year survivors was 74.7%. The mean age at death was 62.7 years (±10.6). The most common causes of death were cardiovascular disease and malignancy. The two major causes of graft loss were death (with function) and interstitial fibrosis/tubular atrophy. Comorbidities included skin cancer (36.1%), coronary heart disease (17.3%) and other malignancies (14.5%). This study identifies factors associated with long-term allograft survival and a high rate of morbidity and early mortality in long-term transplant recipients.

Key words: Cyclosporine, kidney transplant, long-term allograft survival, living-related transplantation

Abbreviations: AZA, Azathioprine; CSA, Cyclosporine; DCD, Donation after Cardiac Death; DDRT, Deceased Donor Renal Transplant; DWFG, Death with a Functioning Graft; HLA, Human Leukocyte Antigen; HR, Hazard Ratio; LLRT, Living Related Renal Transplant; PRA, Panel Reactive Antibody.

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Introduction

Renal transplantation is the treatment of choice for end-stage renal failure. Improvements in short- and long-term graft and patient survival continue to be made (1,2,3). These improvements can be attributed to advances in microbial prophylaxis, surgical techniques, immunosuppressive therapy and histocompatibility testing.

Long-term graft survival, however, has not improved to the same degree as short-term survival (4,5). Recently, Lamb et al. demonstrated that graft half-life had improved from 6.6 years in 1989 to 8.2 years in 2000, mostly due to dramatic improvements in 1-year graft survival (5).

We, and others, have previously reported on our experience of 10-year survivors of kidney transplantation (6,7). However due to the lengthy follow-up necessary, there is a paucity of literature about the truly ultralong-term survivors of transplantation, i.e. patients who have had a functioning kidney transplant for in excess of 20 years.

The aim of this study was to identify clinical factors associated with 20-year kidney allograft survival in a large single center cohort and to determine the prevalence of comorbidities in this patient group.

Patients and Methods

We conducted a retrospective analysis of all kidney transplants performed between January 1, 1970 and August 1, 1991. All kidney transplants in Ireland were carried out in the Charitable Infirmary prior to 1987 and in Beaumont Hospital after 1987. The patient demographic data were available from our renal patient database (Clinical Vision 3.4a Version 1.1.34.1, Clinical Computing, Cincinnati, OH, USA). Follow-up analysis was until August 1, 2011.

All transplants were ABO compatible and had negative cross-matches on complement dependent cytotoxicity assays. HLA identical status was defined as O mismatches at HLA A and B loci in the 1970s and extended to HLA A, B and DR loci in the 1980s. Between 1970 and 1983, all deceased donors were donated after cardiac death (DCD) (Maastricht type 3 and 4). As all transplants are performed at a single center and there are a limited number of transplant surgeons, there was uniformity of care and treatment protocols. Protocol biopsies were not performed.

Initial Medications

All patients were treated with intravenous methylprednisolone 500 mg daily for 3 days followed by prednisolone 20 mg daily. Only 24 patients received induction therapy with ATG. Prior to 1986, all patients were initially treated with azathioprine and prednisolone. After 1986, all patients were treated

with cyclosporine (4 mg/kg twice daily), azathioprine (2 mg/kg) and prednisolone. Cyclosporine doses were adjusted to achieve troughs of 200–250 ng/mL in the early posttransplant period, with maintenance levels of 120–180 ng/mL after 6 months. Acute rejection refers to rejection occurring within the first 3 months after transplant. Acute rejection (AR) episodes were treated with intravenous methylprednisolone and in some resistant cases OKT3. The indications for a renal transplant biopsy were a rise in the serum creatinine of >/= 15–20% from the baseline level (in the absence of any other clear clinical explanation). Coronary heart disease was the need for revascularization (PCI or CABG) or myocardial infarction.

Statistical Analysis

Wilcoxon rank-sum and Pearson chi-squared tests were used to assess demographic differences in 20-year survivors for continuous and categorical variables respectively. Kaplan–Meier analysis was used to determine survival probabilities at various times posttransplant. Both first and subsequent transplants were used for graft survival (however a single graft functioning for 20 years was considered 20 year kidney allograft survival). Time from the first transplant was used for patient survival. The Wilcoxon (Breslow) test for equality of survivor functions was used to compare graft survival outcomes between various groups. All causes of graft failure including death with a functioning graft were analyzed. Cox proportional hazards models were used to assess predictors of long-term survival for both patient and graft outcomes. Factors statistically significant on univariate analysis were included in a multivariate analysis. The assumption of independence of observations is potentially undermined by the inclusion of multiple patient entries due to second or subsequent transplants. To address this point, the Cox models used clustering of individual patients stratified by transplant number to obtain robust standard errors on the hazard ratios. There was insufficient follow-up data on six patients after the 20-year time point and they were not included in the analysis of comorbidities. Stata (version 10, College Station, TX, USA) was used to analyze the data. A p value of less than 0.05 was deemed to be significant.

Results

Patient characteristics

There were a total of 1253 transplants in 1081 patients performed at our center prior to August 1, 1991. Of these, 48 transplants were performed between 1964 and 1969, most of who failed early and were excluded from the study. A further 31 patients that were lost to follow up immediately after procedure were also excluded leaving 1174 transplants for 1002 patients in the study. Figure 1 is a flow chart of patients.

Of these 1174 transplants, 255 (21.72%) grafts survived greater than 20 years. There were 44 patients with a kidney transplant functioning for more than 30 years. Table 1 describes the baseline demographic information for patients. Patients are grouped according to whether their transplant functioned for less than 20 years (nonsurvivors) or more than 20 years (survivors). Causes of end-stage renal failure included glomerulonephritis (24%), chronic pyelonephritis (17%), inherited kidney disease (11%), other causes (21%) and unknown (27%) reflecting a different epidemiology to that of today. Of those whose transplant failed prior to 20 years, the most common cause was death with a functioning graft (38.6%), followed by chronic allograft nephropathy (35.2%).

Long-term patient and graft survival for DDRT and LRRT are presented in Table 2. Acute rejection in the first 3 months occurred in 58.4% of nonsurvivors and 49% of survivors

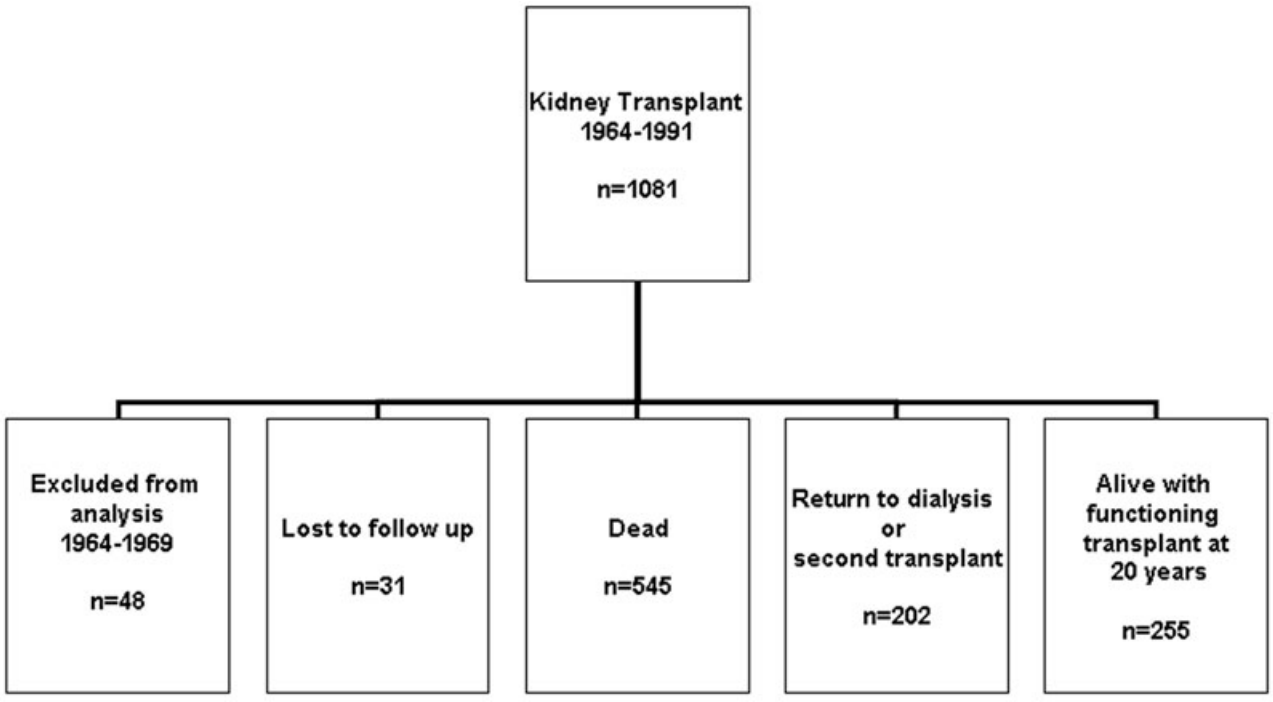

Figure 1: Patient flow in 1253 transplant recipients.

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Table 1: Demographic characteristics of patients

Variable	Nonsurvivors	Survivors	p-Value
Recipient age (mean± SD)	38.46 ± 14.78	31.16 ± 10.90	<0.001
Donor age (mean ±SD)	30.11 ± 15.06	27.64 ± 12.33	0.107
Recipient sex (male)	68.34%	60.00%	0.013
Donor sex (male)	62.16%	63.26%	0.772
Cold ischemia time (h)	19.33 ± 7.13	19.05 ± 7.33	0.592
Number of HLA mismatches (mean)	1.91 ± 1.21	1.39 ± 1.25	<0.001
Living-related donor	6.96%	26.27%	<0.001
Immunosuppression[1]	47.88%	60.00%	0.001

[1]Azathioprine-based immunosuppression as opposed to cyclosporin-based immunosuppression.

($p = 0.01$). 88% of cases of acute rejection were biopsy proven. The 20-year kidney allograft survival according to era of transplantation for the 1970s, 1980s and 1990s was 18.5%, 23.5% and 19.6%, respectively.

Factors associated with long-term allograft survival

While there were more male recipients with 20-year graft survival, this simply reflects the fact that there were more males transplanted. Female recipients were significantly more likely to survive 20 years compared to male recipients with 20-year graft survival rates of 102/393 (25.95%) versus 153/781 (19.59%), respectively ($p = 0.01$).

Similarly, 67/131 (51.4%) of living-related renal transplants (LRRT) survived 20 years compared to 188/1043 (18.02%) of deceased donor renal transplants (DDRT) ($p < 0.001$). Table 2 illustrates the survival advantage of LRRT up to 20 years of follow-up. Of living-related kidney transplants, 68.7% were HLA identical (as assessed by previous methods).

In unadjusted analysis, 25.8% of kidney transplant treated with azathioprine ($n = 593$) survived 20 years compared to 17.6% of patients treated with cyclosporine ($n = 581$) and low dose azathioprine ($p = 0.001$). However, patients maintained on azathioprine-based immunosuppression were more likely to have had a living-related donor and fewer HLA mismatches. Thus, we performed a survival analysis for kidney allograft survival adjusted for immunosuppression type, adjusted for recipient age, sex, the number of HLA mismatches, transplant number and transplant type (Figure 2). Cyclosporine use resulted in improved short- and long-term graft survival compared to azathioprine.

Cox proportional hazard models were used in univariate and multivariate analysis. Results for univariate regression are listed in Table 3.

Variables that retained significance for long-term graft survival independent of potential confounders are presented in a parsimonious model below (Table 4).

We identified younger recipient age, female recipient, having a living donor and the absence of acute rejection as being associated with 20-year renal allograft survival.

Allograft function in 20-year survivors

Median creatinine was 115 μmol/L (interquartile range 99–162 μmol/L). Figures 3A and B demonstrate the graft survival and death censored graft survival, respectively, of the 20-year survivors (i.e. after the 20 year time point). The 5-year graft survival in 20-year survivors was 74.7%. Thirty-eight of the 255 patients who survived to 20 years died during the follow-up. Causes of death are listed in Table 5. The mean age at death was 62.7 years (±10.6). The majority of deaths (32/38) were death with graft function. Median creatinine at 20 years in patients who subsequently died was 114.5 μmol/L. Mean time to death following transplant was 24.1 years (±4.1).

Seventy one of the 255 transplants failed during the follow-up period. The median creatinine at 20 years in those

Table 2: Long-term survival (%)

Time after transplant	Deceased donor transplants	Living-related transplants	Overall transplants
(a) Patient survival			
5 years	71.9 (68.6–74.8)	88.6 (81.2–93.2)	73.9 (71.0–76.7)
10 years	56.9 (53.3–60.3)	80.5 (71.6–86.9)	59.8 (56.5–63.0)
15 years	42.4 (38.7–46.0)	73.2 (63.4–80.7)	46.2 (42.8–49.6)
20 years	31.9 (28.3–35.5)	68.9 (58.8–76.9)	36.7 (33.3–40.1)
(b) Actual graft survival			
5 years	54.5 (51.5–57.5)	74.8 (66.5–81.4)	(53.9–59.6)
10 years	37.5 (34.5–40.4)	61.1 (52.2–68.8)	(37.3–42.9)
15 years	25.6 (23.0–28.3)	54.2 (45.3–62.3)	28.8 (26.2–31.4)
20 years	18.1 (15.8–20.5)	51.1 (42.3–59.3)	21.8 (19.5–24.2)
(c) Death censored graft survival (%)			
5 years	65.6 (62.5–68.5)	80.3 (72.3–86.3)	67.3 (64.4–70.0)
10 years	54.7 (51.4–57.9)	70.4 (61.5–77.6)	56.6 (53.5–59.5)
15 years	45.3 (41.8–48.7)	65.9 (56.7–73.5)	47.9 (44.7–51.1)
20 years	38.0 (34.5–41.6)	64.0 (54.7–71.9)	41.7 (38.3–44.9)

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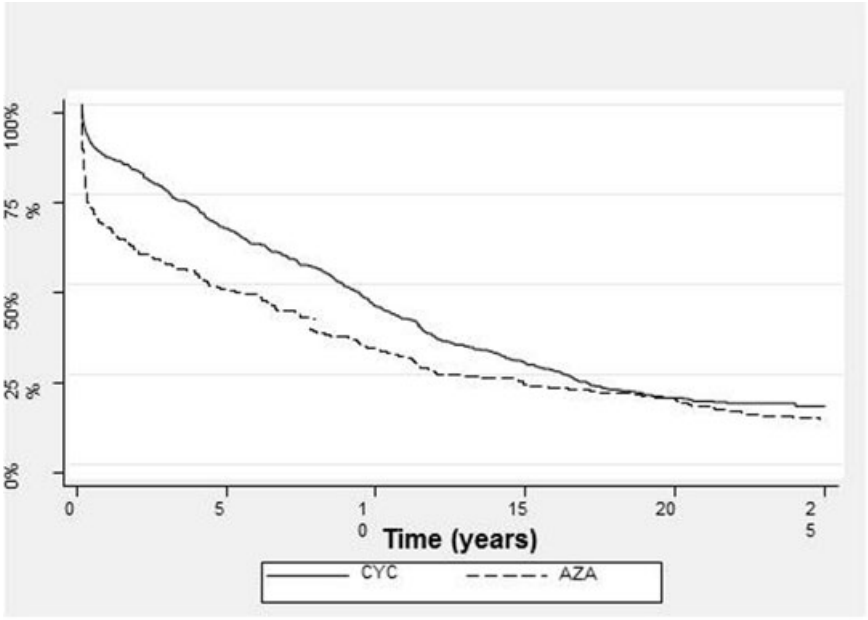

Figure 2: Graft survival based on immunosuppression type, adjusted for recipient age, sex, number of HLA mismatches, transplant number and transplant type. CYC = cyclosporine; AZA = azathioprine.

whose transplant subsequently failed was 174 μmol/L. Causes of graft failure are listed in Table 6. Most graft losses were due to death (DWFG) and interstitial fibrosis/tubular atrophy (chronic allograft nephropathy). DWFG represented 38% of graft loss in the nonsurvivors compared to 45% in 20-year survivors.

Table 3: Univariate Cox regression model indicating factors significant for long-term graft loss

Variable	Hazard ratio	95% Conf. interval	p-Value
Recipient age (years)	1.016	[1.011–1.020]	<0.001
Recipient sex (male)	1.229	[1.074–1.406]	0.003
Donor age (years)	1.005	[0.999–1.009]	0.074
Donor sex (male)	0.929	[0.799–1.081]	0.341
HLA mismatches (mean)	1.162	[1.090–1.238]	<0.001
Acute rejection	1.316	[1.146–1.512]	<0.001
PRA[1]	0.985	[0.897–1.081]	0.749
Transplant type (LRD)	0.430	[0.340–0.545]	<0.001
CIT[2]	0.992	[0.980–1.004]	0.192
IST[3]	0.948	[0.831–1.081]	0.423

[1]PRA groups (0–10%, 11–49%, 50–100%).
[2]Cold ischaemic time (h).
[3]Azathioprine based immunosuppression as opposed to cyclosporine based.

Table 4: Multifactorial Cox regression model indicating factors significant for long-term graft loss

Variable	Hazard ratio	95% Conf. interval	p-Value
Recipient age (years)	1.013	[1.008–1.018]	<0.001
Recipient sex (male)	1.234	[1.063–1.432]	0.006
Transplant type (LRD)	0.510	[0.393–0.663]	<0.001
Acute rejection	1.248	[1.088–1.431]	0.002

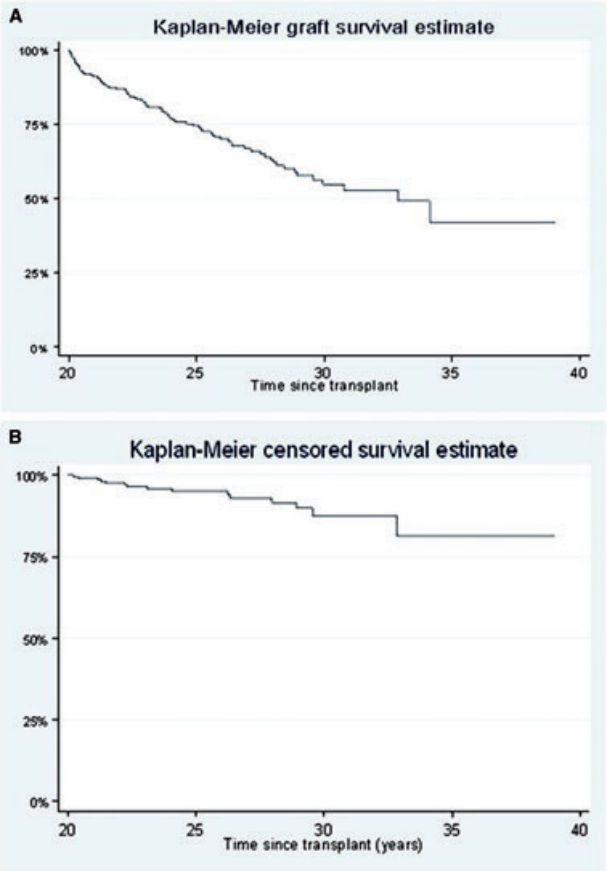

Figure 3: (A) Graft survival of all 20-year survivors. (B) Death censored graft survival of all 20-year survivors.

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Table 5: Primary causes of death after 20 years

Causes of death	n (%) Total = 38
Cardiovascular	12 (31.6%)
Cardiac	6 (15.8%)
CVA	4 (10.5%)
Other	2 (5.3%)
Infection	1 (2.6%)
Malignancy	11 (28.9%)
Pulmonary embolus	1 (2.6%)
Unknown	13 (34.2%)

Table 6: Causes of graft failure in 20-year survivors

Causes of graft failure	N (%) Total = 71
Death	32 (45.1%)
Interstitial fibrosis/tubular atrophy	28 (39.4%)
Recurrence of primary disease	1 (1.4%)
Noncompliance	1 (1.4%)
Other[1]	4 (5.6%)
Unknown	5 (7%)

[1] Infection, prerenal.

Immunosuppression

Median creatinine in patients on cyclosporine-based and azathioprine-based immunosuppression was 146 μmol/L (interquartile range 113–187 μmol/L) and 107 μmol/L (interquartile range 95–127 μmol/L), respectively ($p < 0.001$). There were medication changes in 35 patients, and 18 of these were prior to 20 years posttransplant. Twelve patients in the azathioprine group changed immunosuppression-5 changed to mycophenolate mofetil due to hyperuricemia and the need for allopurinol, 4 switched to cyclosporine and 1 to sirolimus. One patient stopped all immunosuppression due to disseminated infection and the transplant subsequently failed. One HLA identical living donor recipient stopped azathioprine of his own accord and continues to have good allograft function. There were 23 patients in the cyclosporine group who changed medications-5 switched to azathioprine, 8 switched to tacrolimus and 2 to sirolimus. There were eight patients in the CSA group who were on azathioprine in addition to cyclosporine and the AZA was either stopped or switched to mycophenolate mofetil. Median creatinine was higher in the patients who changed medication prior to 20-year time point (180 μmol/L).

Long-term complications

Long-term complications in patients with 20-year allograft survival included coronary heart disease which occurred in 43/249 (17.3%) of patients. The prevalence of coronary heart disease was greater in male than females (32/150 (21.3%) versus 11/99 (11.1%). The rate was similar in LRRT (11/65 or 16.9%) and DDRT (32/184 or 17.3%). A total of 56% of those that suffered from coronary heart disease received revascularization therapies (CABG or PCI). Nonmelanomatous skin cancer occurred in 90/249 (36.1%) of patients. The rate was higher in DDRT (36.9%) versus LRRT (33.8%). Other malignancy, including breast, vulvar, cervical and colon cancer, occurred in 36/249 (14.5%) patients. The rate was higher for females than males 20/99 (20.2%) versus 16/150 (10.7%), respectively. Rates of cancer were 8/65 (12.3%) for LRRT and 28/184 (15.2%) for DDRT.

Of the patients who developed malignancy, 18/36 (50%) subsequently developed graft failure which is higher than the overall rate (71/255 or 27.8%). They also had a higher rate of death (30.5%) versus 14.5% for those without cancer.

Discussion

Patients with kidney failure frequently present at a young age therefore identification of factors associated with long-term transplant survival represents an important area for research. As transplantation has evolved, it is only in the last few years that a large number of patients have experienced truly long-term graft survival. This is the first large study to describe the outcome of kidney transplantation 20 years later.

Our study confirms the survival advantage associated with LRRT (Table 2). In our group, 69% of LRRT were HLA identical, and the majority was maintained on azathioprine-based immunosuppression. These factors, in combination with other factors such as minimal cold ischaemia times, contribute to the survival benefit of LRRT. The overall mean number of HLA mismatches in our patients is lower that in other series. The mean number of HLA mismatches in the nonsurvivors group is 1.91 ± 1.21 compared to 1.39 ± 1.24 in the 20-year survivors.

Multivariate analysis found that female recipients were significantly more likely to experience 20-year kidney allograft survival. Meier-Kriesche et al. previously found that female recipients have better 8 year graft and patient survival however death-censored graft survival was similar between males and females (8). To our knowledge, we are the first to demonstrate superior 20-year graft survival in female recipients. We did not find donor age to be significant. In the current era, donor age has been shown to influence short-term graft outcomes however in the 1970s and 1980s donors were younger (9,10).

There was a dramatic improvement in graft survival between the 1970s and 1980s. This did not continue into the 1990s and this may be due to the fact that older and higher risk patients were being transplanted in addition to the use of expanded criteria donors. Also, the number of patients transplanted in the 1990s in our study population was small as only patients transplanted prior to 1991 were included.

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Acute rejection was shown to be associated with a greater risk of graft failure by 20 years on both univariate and multivariate analysis (Table 3 and 4). It is interesting to note however, that there was a history of early acute rejection in 49% of 20-year transplant survivors, and so, even in the setting of acute rejection, ultra long-term graft function is possible.

Patients treated with cyclosporine had greater short-term graft survival due to a reduction in acute rejection. However, although our study was not controlled to specifically address the long-term benefits of cyclosporine, the survival advantage of cyclosporine became less apparent with time. This follows adjustment for the fact that more patients in the azathioprine group are LRRT and HLA identical. Patients in the CSA group also had significantly higher median creatinine compared to the AZA group. In the long term, CSA use may cause glomerular sclerosis, arteriolar hyalinosis and tubular atrophy and interstitial fibrosis (11). Gallagher et al. (12) previously reported on 20-year follow-up of patients treated with cyclosporine. Patients were randomized to three immunosuppressive regimes: azathioprine and prednisolone, long-term cyclosporine alone, or cyclosporine initiation followed by withdrawal at 3 months and azathioprine and prednisolone replacement. At 20-year follow-up, the mean graft survival was 14.8 years for the short-term CSA group compared to 12.4 years and 12.5 years for the azathioprine and long-term cyclosporine groups respectively. In our study, it was not until 20 years that cyclosporine treated patients had a similar rate of graft loss to azathioprine treated patients.

Five-year graft survival in 20-year survivors (after the 20 year time point) was 74.7% and this is comparable to the general transplant population (13). Death with a functioning graft represented an increasing cause of graft loss (Figure 3B). There was a high rate of malignancy in the transplant patients and malignancy was associated with a higher mortality and rate of graft loss. We have previously demonstrated an increasing cumulative incidence of cancer with an increased duration posttransplant (14). Berehi et al. recently published data on a 56 patients with 30-year transplant survival (15). They demonstrated a prevalence of 46% and 28% for skin cancer and nonskin cancer, respectively.

Matas et al. (7) previously analyzed complications in 2202 kidney transplant recipients with 10-year allograft function. By 20 years, the prevalence of skin cancer, coronary heart disease and other malignancy was >40%, >30% and >10%, respectively. Our study found lower rates of comorbidities. Matas study included patients whose transplant had failed and who were at higher risk of complications. Gallagher et al. followed 489 transplant recipients randomized to three different immunosuppression regimens with a median follow-up 20.6 years for survivors. They found rates of skin cancer and nonskin cancer of 35% and 19%, respectively (16) which are similar to the findings in our study.

Our study has several limitations. Firstly, it is a single center study and has the limitations inherent to any such study. However, we do have comprehensive follow-up on a large proportion of patients over a prolonged period. Second, the characteristics of the 20-year survivors we have described reflect a survivor bias in a population of patients with a lower risk of graft failure and comorbidities. Finally, our immunosuppression protocols have changed over time. Mycophenolate mofetil replaced azathioprine in 1994 and we have used tacrolimus instead of cyclosporine since 2001. Calcineurin inhibitor exposure is now lower than it was previously.

This study is the largest single center study to date examining long-term outcomes of transplant at 20 years. We identified several clinical factors associated with 20-year kidney allograft survival. There is a high rate of morbidity in the third decade posttransplant. As increasing numbers of patients are transplanted, and graft survival improves, physicians will encounter greater numbers of patients with long-term exposure to immunosuppression. Use of a living donor, implementation of appropriate prevention measures and early diagnosis and treatment of long-term complications may further improve long-term transplant survival.

Collaborators

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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